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Appendectomy and Protection against Ulcerative Colitis

To the Editor: Like prior case–control studies, a follow-up study from Sweden (March 15 issue)[1] reported that appendectomy is associated with a low risk of subsequent ulcerative colitis. These findings have led to speculation about causality, suggestions that appendectomy might be therapeutic, and even proposals that appendectomy be performed prophylactically in first-degree relatives of patients.[2] These are not trivial conclusions. However, the literature on this subject is fraught with methodologic problems,[3] some of which are also present in the study by Andersson et al.[1]

Andersson et al. excluded 294 patients with ulcerative colitis that occurred at or before or within one year after the appendectomy, as compared with 192 of the controls — a difference of 102. That there was an excess number of case patients with ulcerative colitis who were excluded most likely occurred because patients with ulcerative colitis, whether established or incipient, can have symptoms so suggestive of appendicitis that surgery is indicated. It is not surprising that when outcomes among subjects with the exposure variable under evaluation, in this case appendectomy, are excluded from the study, a protective effect for that exposure is found in the remaining subjects.

Notably, the excess of 102 almost exactly matches the difference in the number of cases of ulcerative colitis reported during follow-up (304 among the case patients and 410 among the controls; a difference of 106), leaving the total number of cases of ulcerative colitis virtually identical in the two groups (598 and 602, respectively). Hence, the finding by Andersson et al. of an inverse association of appendectomy with the risk of ulcerative colitis can be accounted for by their exclusion policies. In a cohort study that addressed the same issue, we found no association between ulcerative colitis and appendectomy in 154,434 Danish patients who had undergone appendectomy.[3] In our view, there is also no effect of appendectomy on the risk of ulcerative colitis in the data analyzed by

Andersson et al.

Morten Frisch, M.D., Ph.D.
Statens Serum Institut
DK-2300 Copenhagen, Denmark
mfr@ssi.dk

Robert J. Biggar, M.D.
National Cancer Institute
Rockville, MD 20852

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To the Editor: The study by Andersson et al. strengthens the evidence that appendectomy is associated with a low risk of subsequent ulcerative colitis. Some aspects of the study, however, deserve comment. First, the mean age at the diagnosis of ulcerative colitis seems older (33.7 years) than the one usually reported in Scandinavian countries. Indeed, the first peak in the incidence of ulcerative colitis occurs between the ages of 20 and 25 years in Western countries.[1] Another report stated that the median age at diagnosis is 12.2 years in Sweden.[2] Could the authors have missed a significant number of patients?

A second concern is the lack of data on smoking status. Along with appendectomy, smoking has been repeatedly reported to confer protection against ulcerative colitis.[3] Thus, it may be an important confounding factor. A significant association between acute appendicitis and smoking in adults and passive smoking in children has been reported.[4]

Jean Louis Frossard, M.D.
Raymond de Peyer, M.D.
Antoine Hadengue, M.D.
Geneva University Hospital
1211 Geneva 14, Switzerland
jean-louis.frossard@hcuge.ch

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To the Editor: Andersson and coworkers suggest that appendectomy protects against ulcerative colitis, but only if it is performed before the age of 20 years. The alternative hypothesis — namely, that ulcerative colitis protects against appendicitis — is also attractive. Ulcerative colitis involves the mucosal lining of the bowel, and appendiceal lesions are common, especially in patients with less extensive colonic disease.[1] Destruction of the mucosal lining of the appendix in patients with ulcerative colitis could cause fibrosis and obliteration of the appendix, reducing the risk of subsequent obstructive appendicitis. Pathological changes, including fibrosis, were found in more than half of appendixes in patients undergoing colectomy for ulcerative colitis.[2]

If ulcerative colitis protects against appendicitis by inducing fibrosis within the appendiceal lumen, it would explain why the apparent protection of appendectomy against ulcerative colitis in the study by Andersson et al. was limited to younger patients. In the general population, the frequency of appendiceal fibrosis increases with age and might be similar to that in patients with ulcerative colitis.

Albert B. Lowenfels, M.D.
New York Medical College
Valhalla, NY 10595
lowenfel@nymc.edu

Patrick Maisonneuve, Eng.
European Institute of Oncology
20141 Milan, Italy

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The authors reply:

To the Editor: The hypothesis that ulcerative colitis protects against appendicitis, suggested by

Lowenfels and Maisonneuve, has been proposed by others who did not consider the temporal relation between appendectomy and ulcerative colitis. This interpretation of our results is not valid, since we selected patients whose appendectomy preceded their diagnosis of ulcerative colitis. In fact, the larger number of case patients with a diagnosis of ulcerative colitis before or at the time of appendectomy than of controls suggests that ulcerative colitis is a risk factor for appendicitis and appendectomy. This is also consistent with the findings of appendiceal inflammation in patients who underwent colectomy for distal ulcerative colitis.[1]

In response to the comments of Frisch and Biggar, we think it is correct to exclude patients in whom the study outcome has occurred before or at the time of the exposure. Similarly, in order to exclude patients who had undiagnosed ulcerative colitis at the time of the appendectomy, we also chose to start the follow-up one year after the operation.

We have reviewed our results and found one error in Table 1. Thirty-nine of the 74 case patients who were identified as having received a diagnosis of ulcerative colitis within the first year after the appendectomy had actually already been given the diagnosis at the time of the operation. The correct number of exclusions because of a diagnosis of ulcerative colitis before or at the time of appendectomy is therefore 259 case patients (instead of 220) and 168 controls.

We recalculated our results, starting the follow-up immediately after the appendectomy and including the 35 case patients and 24 controls who had been given a diagnosis of ulcerative colitis within one year after the operation. We found little change. The incidence-rate ratio of ulcerative colitis among the patients who underwent appendectomy for appendicitis as compared with the controls was 0.77 (95 percent confidence interval, 0.65 to 0.90); after appendectomy for mesenteric lymphadenitis it was 0.56 (95 percent confidence interval, 0.32 to 0.94); and after appendectomy for nonspecific abdominal pain it was 1.34 (95 percent confidence interval, 0.79 to 2.30). For the patients who underwent surgery for appendicitis before the age of 20 years it was 0.45 (95 percent confidence interval, 0.33 to 0.61), and for patients who underwent surgery at or after the age of 20 years it was 1.00 (95 percent confidence interval, 0.81 to 1.22).

Frossard et al. comment on the age at diagnosis of ulcerative colitis, which is older in our study than in other studies of ulcerative colitis. Since we included only patients who had received a diagnosis of ulcerative colitis more than one year after the appendectomy, the mean age at the start of follow-up was 23.1 years. In addition, had information regarding whether or not the subjects smoked been available, we believe it would have marginally affected our results. This has been the result in previous studies in which an adjustment for smoking status was made.[2,3,4,5]

Roland E. Andersson, M.D., Ph.D.
Ryhov Hospital
S-551 85 Jönköping, Sweden
roland.andersson@ryhov.ltjkpg.se

Anders Ekbom, M.D., Ph.D.
Karolinska Institute
S-171 77 Stockholm, Sweden

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